FULL LENGTH ARTICLE

Echocardiographic evaluation of left ventricular diastolic and systolic function in Saudi patients with sickle cell disease

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Background and objectives: **Sickle cell disease (SCD) is a chronic, inherited haemoglobin disorder, associated with recurrent vaso-occlusive and haemolytic crises and chronic tissue ischemia which may adversely affect any organ system. Our objectives were to evaluate the left ventricular (LV) systolic and diastolic functions in Saudi patients with SCD originally from the Eastern Province of Saudi Arabia.**

Design and setting: **Prospective hospital based echocardiography study on adolescent and adult patients with SCD.**

Methods: **Forty-five patients with SCD were recruited for echocardiographic study while 45 patients, matched for age and sex, served as controls. Left and right ventricular dimensions and LV wall thicknesses, LV mass index (LVMI) and LV contractility variables were obtained. Left atrial dimension and volume and pulmonary artery systolic pressure (PASP) were also estimated. We also evaluated parameters of LV diastolic function, including early and late mitral flow velocities (E and A wave respectively), E/A ratio, deceleration time (MVDT), A wave duration (MVA D), LV isovolumic relaxation time (IVRT), and tissue Doppler velocities, such as lateral annular e' wave, a' wave, e'/a' ratio and E/e' ratio.**

Results: **There were increases in the LV dimensions, LV volumes, stroke volume, and LVMI of the SCD patients. The preload was increased (LV diastolic volume) and afterload was decreased (low diastolic blood pressure). The LVEF was equivalent, though there was evidence of LV diastolic dysfunction in 24%, and pulmonary hypertension (PH) in 40% of the SCD patients. The mean left atrial volume (LAV) was also increased in the SCD patients.**

Conclusion: **LV diastolic dysfunction (heart failure with preserved ejection fraction) and PH may complicate cases of the Arab-Indian haplotype of SCD.**

Abbreviations: MVE vel, mitral valve flow E wave velocity (cm. sec), MVA vel, mitral valve flow A wave velocity (cm. sec), E/A, E wave/A wave ratio, MVDT, mitral valve deceleration time (ms), MVAD, mitral valve A wave duration (ms), TDI, tissue doppler imaging, Lat e', lateral annular e' wave velocity by TDI (cm. sec), Lat a', lateral annular a' wave velocity by TDI (cm. sec), e'/a', e' wave/a' wave ratio, E/e', mitral flow E wave velocity/lateral annular e' wave velocity by TDI

Keywords: Sickle cell disease, Left ventricular diastolic function, Left ventricular systolic function, Tissue doppler imaging

Received 15 January 2012; revised 16 February 2012; accepted 20 May 2012.
Available online 12 June 2012

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Peer review under responsibility of King Saud University.
URL: www.ksu.edu.sa
http://dx.doi.org/10.1016/j.jsha.2012.05.001

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Introduction

The assessment of LV diastolic function should be an integral part of a routine echocardiographic examination, particularly in patients presenting with dyspnea or heart failure. About half of the patients with a new diagnosis of heart failure have normal or near normal global left ventricular ejection fraction (LVEF). These patients are diagnosed with ''diastolic heart failure'' or ''Heart Failure with Preserved Ejection Fraction – HFPEF'' [1].

Sickle cell disease (SCD) is an important autosomal recessive haemoglobin disorder characterized by recurrent episodes of haemolytic and vaso-occlusive crises due to entrapment of red blood corpuscles in the microvasculature leading to ischemia–reperfusion injury and infarction in multiple organ systems. The poorly controlled lifelong hemolytic anemia and recurrent episodes of organ infarction ultimately lead to a progressive systemic vasculopathy and chronic organ failure [2]. The prevalence of homozygous SCD (HbSS) ranges from 1.2% to 2.6% in the Eastern Province of Saudi Arabia [3–6]. Structural studies of DNA suggest that the sickle cell mutation in the Eastern Province of Saudi Arabia and India has arisen as a separate and independent mutation compared with the four different occasions of mutation that took occurred in Africa [7–11]. The prevalence of cardiac involvement in African American adult patients with SCD is up to 82%, ranging from cardiomegaly to congestive heart failure (CHF)] [12–14]. Diastolic dysfunction, as an early marker of cardiac involvement, precedes the development of CHF and is frequently found in paediatric patients with SCD [12–14]. Nonetheless, diastolic dysfunction and pulmonary hypertension both contribute independently to prospective mortality in patients with SCD. Patients with both risk factors have an extremely poor prognosis [15]. It is believed that patients suffering from SCD in the Eastern Province of Saudi Arabia have a milder form of the disease with less frequent complications and a good outcome, due to the interaction between thalassemia and SCD, and the presence of the Arab-Indian haplotype [16]. However, an epidemiological study has shown that the clinical presentation and complications of SCD in Saudi Arabia varies significantly [17]. Unfortunately, only a single report about the cardiovascular manifestation of SCD [18] was found but there was no reported study evaluating left ventricular diastolic function in Saudi patients with SCD. Thus, the main objective of this prospective study was to evaluate the cardiac performance in general, concentrating particularly on left ventricular diastolic function parameters using Tissue Doppler Imaging (TDI) in adolescents and adult patients with SCD whose origins are in the Eastern province of Saudi Arabia.

Subjects and methods

SCD and control patients were recruited after obtaining informed consent from each patient between January 1st 2010 and July 31st 2011. The SCD group consisted of 45 adolescents and young adults (17–40 years) who were originally from the Eastern Province of Saudi Arabia, and who had been followed in the Haematology Clinic at King Fahd Hospital of the University (KFHU), Al-Khobar. Also recruited were inpatients admitted to the medical wards of the same hospital after complete resolution of all the clinical features of acute sickle cell crises. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *priori* approval by the institution's human research committee. The pulse oxy-meter showed normal oxygen saturation for every recruited SCD patient. Patient's charts were reviewed and patients' demographic, clinical and laboratory data were obtained. Patients with SS hemoglobin disease underwent a detailed transthoracic echocardiographic and echo-Doppler evaluation while in a clinical stable state. Patients were excluded from this study if they were on chronic transfusion therapy or if they have received recent blood transfusion, had hemoglobinopathies other than SCD, had known congenital or acquired cardiac or pulmonary diseases, electrocardiographic abnormalities which may affect the interpretation of the echocardiographic findings, or had any medical conditions other than anemia affecting their myocardial performance. Subjects with inadequate acoustic windows were also excluded. The control group consisted of 45 age- and sex matched subjects referred to the echocardiography laboratory with diagnoses of heart murmur, palpitations, or syncope, and found to have normal echocardiograms.

Clinical data

Blood pressure measurements were performed prior to the echocardiogram. Mean hemoglobin (Hb), hemoglobin F (Hb F), and ferritin levels for 1 year preceding the study were calculated.

Echocardiographic examination

All studies were performed using a Diagnostic Ultrasound System, Xario Prime Ultrasound from

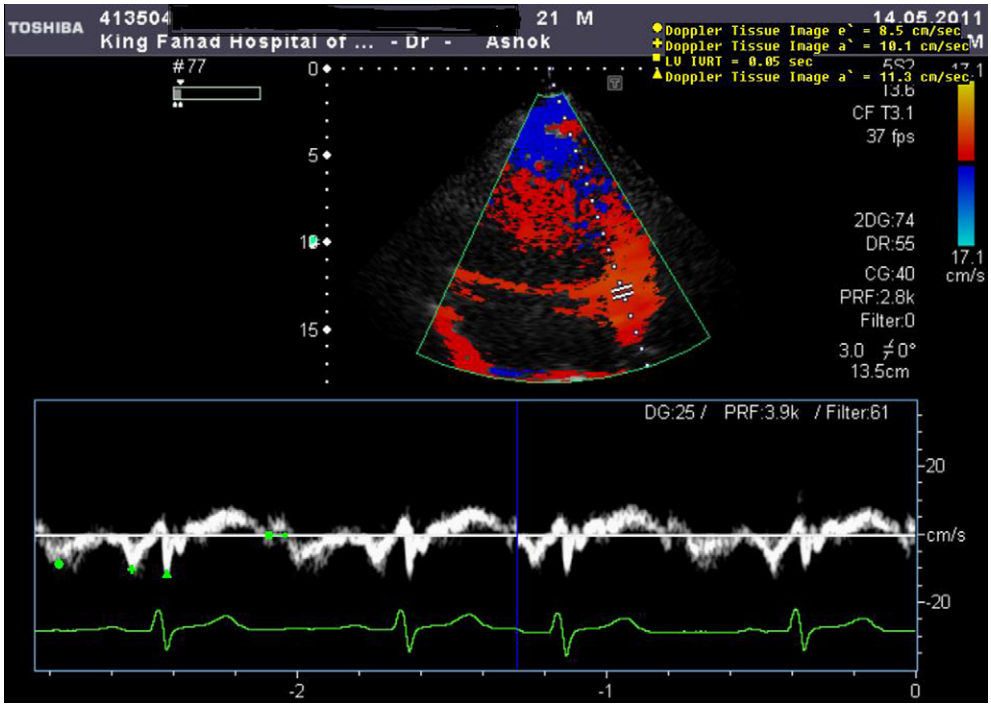

Figure 1. Lateral mitral annular TDI of a SCD patient showing LV diastolic dysfunction (e'/a' ratio of 0.79) in one of the study patients.

Toshiba Medical Systems, Model SSA-660A, equipped with tissue Doppler imaging (TDI) technology. All subjects underwent a complete two-dimensional, spectral Doppler, color Doppler flow, and TDI examination. Echocardiograms were recorded digitally and subsequently analyzed by the use of a digital analysis system (Phillips Xcelera R2.2L.1.SP2; 2.2.1258–2009).

M-Mode measurements

The left ventricular mass (LVM) was calculated using the ASE-cube method in Devereux modification guided by parasternal short axis view [19] and was normalized for the body surface area (BSA) to estimate the left ventricular mass index (LVMI). Systolic function was considered abnormal if the fraction of shortening was less than 28% or LVEF was less than 50%. Pulmonary artery systolic pressure (PASP) was calculated by adding an assumed right atrial pressure of 10 mm Hg to the regurgitant jet gradient across the tricuspid valve. Pulmonary artery systolic hypertension was defined as PASP > 30 mm Hg [20].

Mitral flow velocity measurements

Transmitral Doppler flow signals were recorded in the apical four-chamber view as described by Rakowski et al.[1,21] Three measurements of each index were performed and averaged for data analysis. Peak mitral flow velocities in early diastole (E) and during atrial contraction (A) were measured. The early/late velocity ratio (E/A) was calculated. Measurement of left atrial volume: LAV was measured by Simpson's method in apical four and two- chamber views and the average was indexed to body surface area (BSA). Timing of the measurement was defined at maximal expansion of the left atrium.

Measurements of myocardial TDI velocities

TDI myocardial velocities were measured in the longitudinal axis from the apical four-chamber view. Myocardial velocities were sampled at the level of the mitral annulus on the lateral aspects as shown in Fig. 1 [1]. The spectral pulsed Doppler studies were recorded digitally. The peak velocities during early diastole (e'), and late diastole (a') were measured and averaged over five consecutive beats. The early mitral inflow/annular movement ratios (E/e') was also calculated [22].

Statistical analysis

Results were expressed as mean ± SD. Each of the variables and ratios in the two studied groups were compared using 2-sample *t*-tests. The Spearman coefficients were used to measure correlation between various patient (demographic and clinical) characteristics and patient outcomes univariately. In a multivariate analysis, stepwise linear regression analysis was performed to explore

potential relations between quantitative variables. For this analysis, Left Ventricular IVRT, left atrial volume index (LAVI), E wave velocity, A wave velocity, E/A ratio, MV dec. time, MVA wave Dur, PASP, lateral annular e', lateral a', e'/a' ratio, and E/e' ratio were chosen as diastolic outcome variables. A *P value* of <0.05 was considered statistically significant for all comparisons.

Results

The demographic and laboratory characteristics of the 45 SCD patients and 45 control subjects are shown in Table 1. The mean (SD) heart rate (HR) was significantly higher in SCD patients than in controls, the mean (SD) systolic blood pressure (SBP) was similar in both groups [119.56 (13.25) mmHg in SCD patients and 120.9 (8.83) mmHg, $p = 0.712$ in controls], whereas, the mean (SD) diastolic blood pressure (DBP) was significantly lower in SCD patients than in controls [69.31 (6.98) mmHg vs.78.67 (4.3) mmHg, $P = 0.003$]. The means (SD) of body weight, height, and BSA and hemoglobin% were significantly lower in SCD patients than in controls, but the mean (SD) ferritin level was much higher in SCD patients than in controls. The means (SD) of LV internal dimensions in diastole and systole (LVIDd and LVIDS), LV end diastolic and end systolic volumes (EDV and ESV), stroke volumes (SV), inter-ventricular septum thickness (IVST), LV posterior wall thickness (LVPWT), and LV mass indexes (LVMI) were significantly increased in SCD patients than in controls, as shown in Table 2 and Fig. 2 [LVIDd = 5.34 (0.41) cm in SCD patients vs. 4.74 (0.46) cm in controls, $p < 0.001$, LVIDs = 3.38 (0.37) cm vs. 3 (0.29) cm, $p < 0.001$, EDV = 139.9 (27.4) ml vs. 108.4 (18.9) ml, $p < 0.001$, ESV = 47.2 (14.7) ml vs. 36.3 (8.3) ml, $p < 0.001$, SV = 92.5 (21.4) ml vs. 72.1 (13.6) ml, $p < 0.001$, IVST = 0.95 (0.12) cm vs. 0.86 (0.15) cm, $p = 0.004$, LVPWT = 0.94 (0.14) cm vs. 0.87(0.12) cm, $p = 0.008$, and LVMI = 122.5 (27.2) g/m^2 vs. 81.7 (19.3) g/m^2, $p = 0.001$], although LV systolic function didn't change [average LVEF = 65.8% (6.6) in SCD patients vs. 67% (5.1) in controls, $p = 0.313$].

Frequency of LV diastolic dysfunction in SCD patients

There was no significant difference between the 2 groups regarding the means (SD) of IVRT, MVDT, MVAD and mitral inflow E/A ratio [IVRT = 66.2 (18.3) msec. in SCD patients vs. 62.7 (23.6) msec. in controls, $p = 0.431$, MVDT = 197.7 (48.3) msec. vs. 203 (50.96) msec. $p = 0.591$, MVAD = 124.9 (32.7) msec. vs.126 (30.8)) msec. $p = 0.763$ and E/A = 1.66 (0.54) vs. 1.79 (0.69), $p = 0.330$] as shown in Table 2. However, there were highly significant differences between the 2 groups in the mean of left atrium volume indexes (LAVI), mean (SD) of lateral mitral annular e' waves, lateral mitral annular a' waves and e'/a' ratio obtained by TDI and E/e' ratio [LAVI = 41.16 ml in SCD vs. 22.65 ml in controls, $p < 0.001$, Lat. e' = 13.5 (2.74) cm/s. vs. 16.13 (3.91) cm/s. $p < 0.001$, Lat. a' = 10.7 (3.9) cm/s vs. 8.2 (2) cm/s, $p < 0.001$, e'/a' = 1.4 (0.4) vs. 2.1 (0.59), $p < 0.001$, and the E/e' = 7.3 (1.6) vs. 5.9 (1.5), $p < 0.001$] as shown in Table 2 and Fig. 2. We found also that 24% of the SCD patients had an e'/a' ratio <1 as an evidence of left ventricular diastolic dysfunction, and a moderate increase in E/e' ratio (between 8 and 15) in 24% of SCD patients which may be considered as a reasonable predictor of increased LV filling pressure as shown in Table 3 and Fig. 2. This increase in the mitral inflow E/e' ratio was powered by the elevated PASP of >30 mm Hg in 18 (40%) of SCD patients as shown in Fig. 3 [mean (SD) PASP of 35.6 (12.09) mmHg in SCD patients vs. 20.08 (3.08) mmHg in controls, $p < 0.001$] and the significantly increased mean LA volume indexes. Of our SCD patients with PH, only five (11.1%) were found to have decreased lateral annular e'/a' ratio <1, and 8 (17.7%) were

Table 1. Clinical characteristics of Sickle Cell Disease Patients versus Normal Control.

Variable	SCD $N = 45$ mean (SD)	Normal control $N = 45$ mean (SD)	*P* value
Age (years)	25.73 (6.79)	27.58 (9.67)	*0.291*
Male gender (%)	82	84	0.293
HR (bpm)	63.53 (6.15)	80.89 (8.23)	<0.001
Systolic BP (mmHg)	120.9 (8.83)	119.56 (13.25)	=0.712
Diastolic BP (mmHg)	78. 67 (4.3)	69.31 (6.98)	=0.003
Weight (kg)	69.36 (10.07)	53.16 (11.68)	<0.001
Height (cm)	167.64 (6.79)	163.02 (5.33)	<0.001
BSA (m^2)	1.77 (0.14)	1.54 (0.170	<0.001
Hb (gm/dl)	14.36 (0.97)	8.60 (1.14)	<0.001
Ferritin level (mcg/l)	123.8 (64.62)	919.4 (1315)	=0.006

Table 2. Echocardiographic and echo-doppler parameters of sickle cell disease patients versus controls.

Echo/doppler variables	SCD patients $N = 45$ mean (SD)	Controls $N = 45$ mean (SD)	P value
(A) *LV structure, volumes and systolic function*			
LVIDd (cm)	5.34 (0.41)	4.74 (0.46)	<0.001
LVIDs (cm)	3.38 (0.37))	3 (0.29)	<0.001
IVST (cm)	0.95 (0.12)	0.86 (0.15)	=0.004
LVPWT (cm)	0.94 (0.14)	0.87 (0.12)	=0.008
EDV (ml)	139.9 (27.4)	108.4 (18.9)	<0.001
ESV (ml)	47.2 (14.7)	36.3 (8.3)	<0.001
SV (ml)	92.5 (21.4)	72.1 (13.6)	<0.001
LVM. I (g/m^2)	122.5 (27.2)	81.7 (19.3)	<0.001
LV. EF (%)	65.8 (6.6)	67 (5.1)	=0.313
(B) *LV diastolic function*			
LV. IVRT (ms)	66.2 (18.3)	62.7 (23.6)	=0.431
LAV (ml)	63.38 (19.23)	40.09 (4.37)	<0.001
LAVI (ml)	41.16	22.65	<0.001
E/A	1.66 (0.54)	1.79 (0.69)	=0.330
MV Dec. Time (ms)	197.7(48.3)	203 (50.96)	=0.591
MV. A Dur. (ms)	124.9 (32.7)	126 (30.8)	=0.763
Lat. e‘ (cm/s)	13.5 (2.74)	16.13 (3.91)	<0.001
Lat. a‘ (cm/s)	10.7 (3.9)	8.2 (2)	<0.001
e‘/a‘	1.4 (0.4)	2.1 (0.59)	<0.001
E/e‘	7.3 (1.6)	5.9 (1.5)	<0.001
(C) *Estimated mean PASP*	35.6 (12.09)	20 (3.08)	<0.001

Table 3. Patients with TDI evidence of LV diastolic dysfunction and patients with combined LV diastolic dysfunction parameters and pulmonary hypertension (PH).

LV diastolic dysfunction	SCD $n = 45$	
	n	%
e‘/a‘ < 1	11	24
E/e‘ > 8	11	24
e‘/a‘ < 1 + PH	5	11.1
E/e‘ > 8 + PH	8	17.7

found to have increased E/e‘ ratio (between 8 and 15) as shown in Table 3 and Fig. 4. Nonetheless, mild mitral regurgitation without structural damage of mitral valve was found in 18 SCD patients (40%) versus 8 (18%) of controls, $p = 0.002$. Using stepwise linear regression analysis, 58.4% of body surface areas (BSA) of SCD patients were explained by ESV, SV, IVRT, LAV, PASP, Lateral annular e‘, lateral annular a‘ and E/e‘. Similarly 54.7% of hemoglobin concentrations in SCD patients were explained by LVPWT, EDV, ESV, SV, IVRT, LAV, e‘, a‘ and E/e‘, and 41.4% of ferritin levels in SCD patients were explained by IVST, LVPWT, EDV, ESV, IVRT, LAV, e‘, a‘ and E/e‘.

Discussion

Tissue Doppler Imaging (TDI) is at the forefront in the transthoracic echocardiographic assessment of LV diastolic function as it is less hindered by preload dependency. Mitral valve annular velocities can be used to draw inference about LV relaxation and along with mitral peak E velocity (E/e‘ ratio) can be used to predict LV filling pressure [21].

To the best of our knowledge, this study represents the first echocardiographic study evaluating both LV systolic and diastolic function in patients suffering from the Arab-Indian haplotype of SCD. In this study, the LV internal dimensions, wall thicknesses, volumes and mass indexes were significantly increased in SCD patients, though the LV ejection fraction was similar in both groups. These cardiac abnormalities are really needed in patients with chronic anemia to increase the cardiac output with little increase in heart rate. However, we found that LV diastolic dysfunction is common in the SCD patients. Our data showed that 24% of SCD patients had lateral mitral annular ‘‘e‘/a‘ ratio <1’’ and in 24% there was evidence of increased LV filling pressure with ‘‘E/e‘ ratio > 8’’. These findings agree with earlier studies of Doppler filling abnormalities,[15,23,24] though the prevalence of LV diastolic dysfunction was higher in our study than that observed by Schdev V. et al., in spite of the lower mean age of our patients in comparison with the mean age in that study (27.6 years vs. 35 years) [15]. In our opinion, the moderate increase in E/e‘ ratio (between 8 and 15) as a predictor of increased LV filling pressure and as a marker of LV diastolic dysfunction is powered by the significant increase in the mean

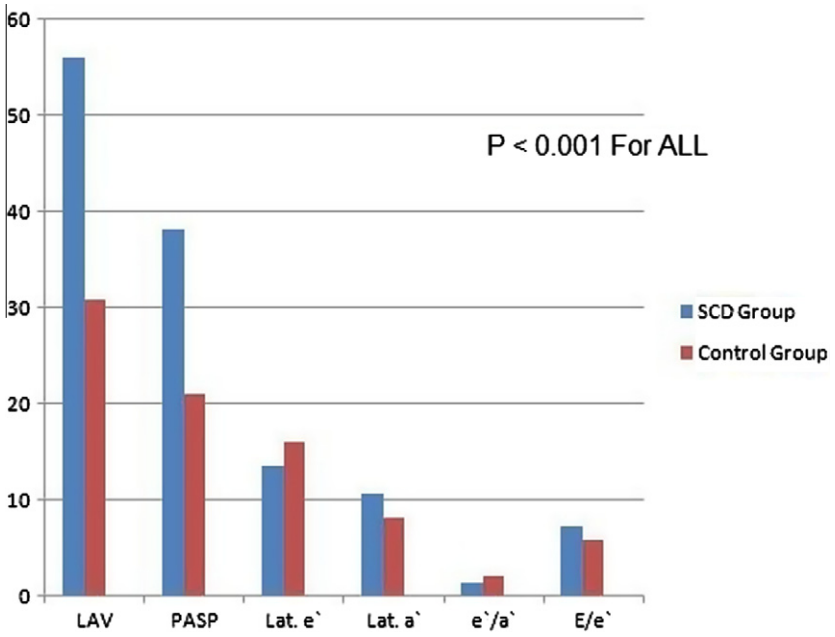

Figure 2. The difference between SCD patients and controls regarding the LV diastolic function parameters.

of LA volume indexes (41.16 ml) and the pulmonary hypertension in 40% of our SCD patients. The prevalence of PH in our SCD patients agrees with the earlier finding of Aleem A et al.[18] We believe that LV diastolic dysfunction was not the only hemodynamic confounder of the significant left atrial dilatation in SCD patients, but may also have been provoked by other factors such as chronic anemia, chronic ischemia-perfusion injury of the atrial walls, and possible iron overload secondary to recurrent hemolytic episodes [1,15]. Similarly, PH was more prevalent in our SCD patients (40%) than LV diastolic dysfunction (24%). This suggests that the LV diastolic dysfunction was not the only hemodynamic cause of PH. Other factors such as chronic vasculopathy, recurrent pulmonary embolization, chronic ischemia-perfusion injury of the lungs, and the chronic high output state associated with SCD also contribute to the development of PH [25–32]. Nonetheless, the exact mechanistic pathways of LV diastolic dysfunction are still uncertain. Though, we are in accord with the opinion that the diastolic dysfunction in SCD patients is mainly due to the recurrent myocardial damage from vascular vaso-occlusive disease and iron overload [15]. Finally, the occurrence of LV diastolic dysfunction and/or PH in SCD patient may be considered an adverse prognostic risk factor for increased mortality [15,32].

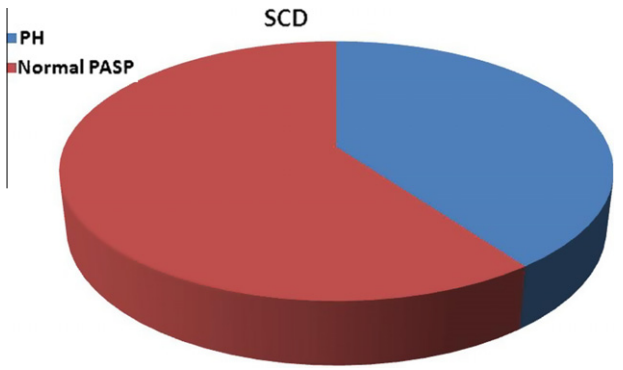

Figure 3. The prevalence pulmonary artery hypertension in SCD patients.

Conclusion

Tissue Doppler Imaging (TDI) has become a very important tool for the diagnosis of LV diastolic function. Therefore, for adolescent and adult patients with SCD, routine echocardiographic studies should be performed as a part of their continuous medical care to identify high-risk patients who may benefit from additional treatment.

Study limitations

The echocardiographic studies should be supplemented with cardiac catheterization for confirmation of PH and pulmonary capillary wedge pressure in high risk patients with SCD.

Conflict of interest

Authors have no conflict of interest to declare.

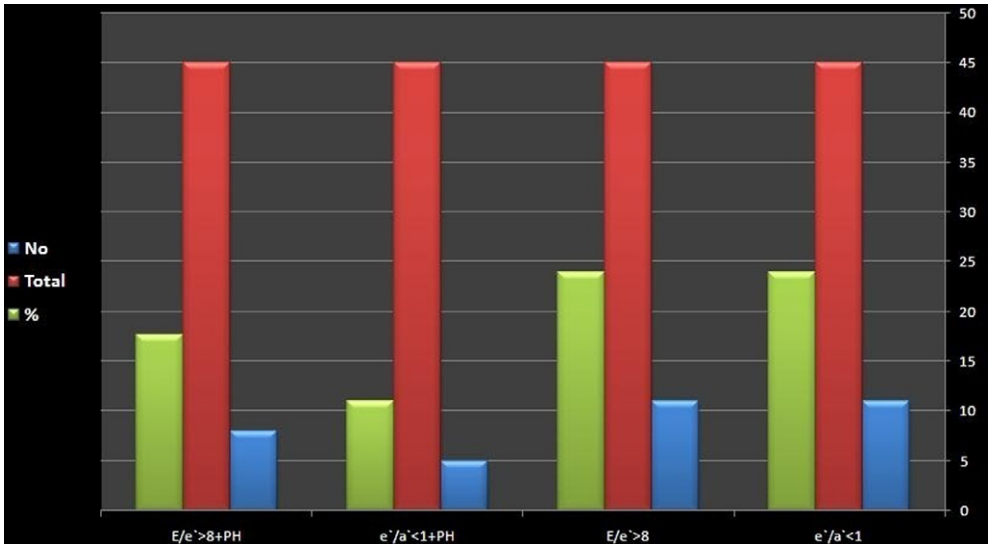

Figure 4. Prevalence LV diastolic dysfunction (DD) among SCD patients and LV diastolic dysfunction when associated with pulmonary hypertension.

Acknowledgements

We would like to express our sincerest appreciation to Dr. Ashok Upadhyaya, physician and echo-cardiographer of King Fahd Hospital of the University for his Remarkable Effort in performing the echocardiographic studies. We are also indebted to Dr. Hany Mowafi, Associate Professor of Anaesthesia, and to Dr. Ammar H. Khamis, Associate Professor of biostatistics, University of Dammam for their contribution in the statistical analysis of this study. We would like also to appreciate the effort of Mrs. Amgad Fakhry, Adel Fakhry and Mr. Ramesh Kumar for secretarial assistance. Finally the editorial review of this manuscript by Professor E. Larbi, Professor of Medicine and Clinical Pharmacology, is greatly appreciated.

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